

***Remarks***

Reconsideration of this Application is respectfully requested.

Claims 10, 11, 25, 26, 40, 41 and 58-63 are pending in the application, with claims 10, 25, 40, 58, 60 and 62 being the independent claims.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

***I. Claim Rejections Under 35 U.S.C. § 112, First Paragraph***

Claims 11, 25, 26 and 58-61<sup>1</sup> were rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. Office Action, page 2. Applicants respectfully traverse this rejection.

The Examiner has made various comments regarding the eight enablement factors set forth in *In re Wands*, 858 F.2d 731, 738 (Fed. Cir. 1988). However, the Examiner has not provided any explanation as to how these factors, taken as a whole, establish that the practice of the methods of the present invention would have required undue experimentation.

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<sup>1</sup> Applicants note that claim 10 is not listed as being rejected under 35 U.S.C. § 112, and that claim 11 is listed twice. Clarification is requested.

As noted in the M.P.E.P. § 2164.01(a), "[t]he examiner's [enablement] analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole." In addition, the Examiner has the burden of establishing a reasonable basis to question the enablement provided for a claimed invention. *See* M.P.E.P. § 2164.04.

Since, here, the Examiner has not provided a clear explanation as to how a consideration of the "Wands factors" leads to a conclusion that the present claims are non-enabled, the rejection under 35 U.S.C. § 112, first paragraph, cannot be maintained. In addition, as discussed below, a proper analysis of the relevant "Wands factors" demonstrates that practicing the claimed methods would *not* have required undue experimentation on the part of one skilled in the art.

***A. Nature of the Invention***

Claims 10, 11, 25, 26 and 58-61 are directed to methods of treating amyloidosis in a subject. The methods comprise administering to the subject a combination of: (a) a chelator specific for copper or a hydrophobic derivative of a chelator specific for the reduced form of copper, and (b) clioquinol.

***B. State of the Prior Art***

There is nothing in the prior art to suggest that it would have required more than routine experimentation to practice the methods of the present invention. For example, as noted in the specification at page 78, line 26, through page 79, line 23, administration of the

metal chelator DFO was shown to attenuate the progression of Alzheimer's disease (AD) in AD patients. In addition, it was known in the art that clioquinol is a hydrophobic metal chelator with a low general toxicity profile and that it crosses the blood brain barrier. *See* specification at page 79, lines 24-28. In addition, it has been demonstrated that clioquinol is rapidly absorbed from the gut of rats and mice. *See* specification at page 80, lines 1-3.

The Examiner has made reference to the specification where it is noted that clioquinol was withdrawn from use as an oral antibiotic for humans in the early 1970s because ingestion of this compound was linked to a condition called subacute myelo-optic neuritis (SMON). *See* Office Action, page 3 (referring to page 80, lines 10-14 of the specification). This, however, does not in any way suggest that the practice of the presently claimed methods would have required undue experimentation. As noted in the specification, the concentration of clioquinol that the present inventors have shown to be effective at resolubilizing A $\beta$  is *lower* than that which was associated with SMON. *See* specification at page 80, lines 26-28. Thus, the incidences of SMON observed when *very high* concentrations of clioquinol were administered for *antibiotic* purposes do not suggest that the use of clioquinol to treat amyloidosis, in accordance with the present invention, would have required undue experimentation.

Finally, a subsequent study (Ritchie *et al.*, *Arch. Neurol.* 60:1685-91 (Dec. 2003), copy attached as Exhibit 1) has shown that clioquinol, when administered to AD patients caused a decrease in plasma A $\beta$ <sub>42</sub> levels. *See* Ritchie *et al.*, page 1688, Figure 3. It was also shown that clioquinol was well tolerated in patients. *See* Ritchie *et al.*, page 1689

(indicating that there were no significant differences in the mean number of attributable adverse events between the test and placebo patient groups). It was further noted by Ritchie *et al.*, that "[t]en subjects have now been receiving [clioquinol] at a dosage of 500 to 750 mg/d for more than 18 months. *No clioquinol-attributable adverse events have developed in any of these subjects.*" *Id.*, page 1690, bottom-right column (emphasis added). The clinical results presented in Ritchie *et al.* confirm that the earlier effects of clioquinol associated with SMON are not indicative of adverse effects when the compound is appropriately administered for the treatment of amyloidosis.

***C. Level of Ordinary Skill in the Art***

Applicants agree with the Examiner that the level of ordinary skill in the art is high.

*See Office Action, page 3.*

***D. Level of Predictability in the Art***

Applicants respectfully disagree with the Examiner's assertion that "the level of the art is not predictable." *See Office Action, page 4.* Applicants also draw the Examiner's attention to the M.P.E.P. § 2164.04, where it is noted that the minimal requirement in making an enablement rejection is for the Examiner "to give reasons for the uncertainty of the enablement," and that "specific technical reasons are always required" to support a *prima facie* case of lack of enablement. Since the Examiner has not provided any support for the assertion that the "the level of the art is not predictable," this assertion cannot legally contribute to a finding of nonenablement.

***E. Amount of Direction and Guidance Provided by Inventors***

The inventors have provided a substantial amount of direction and guidance for practicing the methods of the present claims. For example, the specification provides guidance regarding the formulation and administration of metal chelators. *See* specification at page 21, line 20, through page 31, line 4. Moreover, as discussed below, the specification provides working examples that demonstrate the ability of metal chelators, including clioquinol and bathocuproine (a chelator specific for the reduced form of copper), to resolubilize A $\beta$  from AD-affected brain tissue.

In view of the high level of skill in the art -- as acknowledged by the Examiner, the specification provides more than sufficient guidance for persons skilled in the art to practice the full scope of the claimed methods.

Finally, Applicants note that the Examiner's comments regarding "hopeful, prophetic language" in the specification (*see* Office Action, page 4) are legally irrelevant to the issue of enablement. (Applicants respectfully invite the Examiner to point to any legal authority which suggests that the use of "hopeful, prophetic language" can be used to support a *prima facie* case of nonenablement.)

***F. Existence of Working Examples***

As noted above, the specification provides working examples which illustrate the ability of chelators such as clioquinol and bathocuproine to resolubilize A $\beta$  aggregates. *See* Examples 4-7, pages 71-85. Example 7, in particular, demonstrates that the combination of

clioquinol and bathocuproine caused a significant increase in the degree of A $\beta$  resolubilization from AD-affected brain tissue as compared to controls. *See* specification at page 84, lines 5-25, and Table 4. As noted in the specification, "[t]hese data suggest that combinations of clioquinol and bathocuproine may be particularly effective therapeutic combinations for the treatment of amyloidosis, in particular, the pathological A $\beta$ -aggregation manifest in brains of those afflicted with Alzheimer's disease." *Id.* at page 84, line 25, through page 85, line 3.

The Examiner stated that "there is no *in vivo* testing present in the examples, there are mainly tests done on cadaver brain tissue." *See* Office Action, page 4. Applicants note that, in the field of chelators, *in vitro* experiments are highly indicative of *in vivo* results. As mentioned above, the metal chelator clioquinol has been shown to be effective in the treatment of Alzheimer's disease. *See* Exhibit 1. Clioquinol, like bathocuproine, was first shown to promote the solubilization of A $\beta$  *in vitro*. *See* Cherny *et al.*, *Neuron* 30:665-676 (2001) (copy attached hereto as Exhibit 2). Thus, *in vitro* results with chelators generally, and clioquinol in particular, are indicative of the therapeutic results that are obtained when the chelators are administered *in vivo*. The Examiner's statements regarding *in vivo* testing therefore do not support the enablement rejection.

#### ***G. Breadth of the Claims***

Applicants agree with the Examiner that the claims are drawn to methods of treating amyloidosis. *See* Office Action, page 4. This observation does not suggest that practicing the methods of the claims would have required undue experimentation.

***H. Quantity of Experimentation Needed to Practice the Claimed Methods***

In view of the teachings in the specification and the knowledge possessed by persons of ordinary skill in the art, the practice of the claimed methods would not have entailed an undue amount of experimentation.

The Examiner stated that "the level of experimentation needed on the unpredictable nature of the invention and the extreme breadth of the claims, one skilled in the art could not use the claimed invention without undue experimentation." *See* Office Action, page 4. Applicants respectfully note that this contention on the part of the Examiner is not supported by any specific evidence or sound scientific reasoning and therefore is legally insufficient to contribute to a *prima facie* case of non-enablement.

The only statement set forth in the Office Action to support the contention that "one skilled in the art could not use the claimed invention without undue experimentation," is the unsupported assertion that the "nature of the invention is unpredictable." The Examiner, however, has not provided any indication as to which aspect(s) of the invention are deemed "unpredictable" or in what particular way(s) the invention is deemed "unpredictable." Furthermore, the Examiner's acknowledgement that the claims are drawn to methods of treating amyloidosis does not, by itself, suggest "extreme breadth of the claims." Thus, the Examiner's statements are legally insufficient to support a *prima facie* case of nonenablement.

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

**II.      *Claim Rejections Under 35 U.S.C. § 103***

Claims 40, 41, 62 and 63 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,022,879 to Crow *et al.* ("Crow") in view of U.S. Patent No. 5,980,914 to Gerolymatos ("Gerolymatos"). *See* Office Action, page 5. Applicants respectfully traverse this rejection.

In order to establish a *prima facie* case of obviousness there must be some suggestion or motivation to modify or combine the cited references. *See* M.P.E.P. § 2143. The only explanation for the obviousness rejection provided in the Office Action is the Examiner's comment that "one skilled in the art would have assumed the combination of two individual agents known for their anti-degenerative effects into a single composition would give an additive effect in the absence of evidence to the contrary." *See* Office Action, page 5. Applicants respectfully submit that this assertion is insufficient to establish a *prima facie* case of obviousness.

First, the Examiner has not provided any evidence to indicate what one of ordinary skill in the art may or may not have "assumed" regarding the content of Crow and/or Gerolymatos. In particular, the Examiner has not pointed to anything to indicate that one skilled in the art would have "assumed" that combining bathocuproine and clioquinol would have produced an additive effect. Indeed, the Examiner has not pointed to anything in either reference that would have suggested combining clioquinol with bathocuproine (or *vice versa*), or that these chelators should be combined with *any* other active ingredient, much less another chelator.

Second, the Examiner has not pointed to any particular evidence to suggest that one of ordinary skill in the art would have been motivated to obtain an "additive effect" under any circumstances. Applicants respectfully draw the Examiner's attention to the M.P.E.P. § 2143.01, where it is explicitly stated that:

A statement that modifications of the prior art to meet the claimed invention would have been "well within the ordinary skill of the art at the time the claimed invention was made" because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references.

Here, the obviousness rejection is based on nothing more than an assertion that bathocuproine and clioquinol were *individually* known in the art. There is no *objective reason* why one of ordinary skill in the art would have been motivated to combine these chelators. As the above-quoted language from the M.P.E.P. makes clear, the Examiner's explanation for the § 103 rejection is insufficient to establish a *prima facie* case of obviousness.

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 103 be reconsidered and withdrawn.

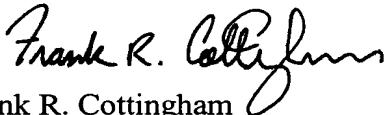
***Conclusion***

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

  
Frank R. Cottingham  
Attorney for Applicants  
Registration No. 50,437

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1100 New York Avenue, N.W.  
Washington, D.C. 20005-3934  
(202) 371-2600

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